

EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Zeldis	Confirmation No.:	1866
Serial No.:	10/699,110	Art Unit:	1612
Filed:	October 30, 2003	Examiner:	Fay, Zohreh A.
For:	METHODS FOR THE TREATMENT AND MANAGEMENT OF MACULAR DEGENERATION USING CYCLOPROPYL-N-;2-((1S)- 1-(3-ETHOXY-4- METHOXYPHENYL)-2- (METHYLSULFONYL)ETHYL)-3- OXOISOINDOLINE-4- YL;CARBOXAMIDE	Attorney Docket No: (CAM:	9516-083-999 501872-999082)

DECLARATION BY PETER H. SCHAFER, PH.D. UNDER 37 C.F.R. 1.132

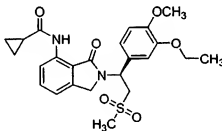
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Peter H. Schafer, Ph.D., declare and state that:

1. I received my Bachelor of Science degree in Biological Chemistry from University of Chicago, Chicago, Illinois in 1991. I received my Ph.D. degree from the Department of Biochemistry, Molecular Biology, and Cell Biology at Northwestern University, Evanston, Illinois in 1996.
2. From 1996 to 1999, I was a post-doctoral researcher at The R.W. Johnson Pharmaceutical Research Institute in Raritan, New Jersey. From 1999 to present, I have been employed by Celgene Corporation, Summit, New Jersey, as a Research Scientist, a Senior Research Scientist, a Group Leader, an Associate Director of Biology, and then as a Director of Biology in the Department of Drug Discovery at Celgene Corporation. Currently, I hold the position of Director of Translational Development at Celgene.

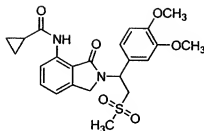
3. I have published in peer-reviewed journals and made presentations at various academic conferences. I am also a named co-inventor of several patents and patent applications owned by Celgene Corporation and relating to immunomodulatory compounds and phosphodiesterase IV ("PDE IV") inhibitors.
4. I have been serving as a reviewer for journals such as Journal of Pharmacology and Experimental Therapeutics, Life Sciences, and Clinical Medicine: Therapeutics.
5. I am familiar with the disclosure and claims of the above-identified patent application ("the '110 application"). I understand that the pending claims recite, *inter alia*, methods of treating macular degeneration, comprising administering a therapeutically effective amount of cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindoline-4-yl}carboxamide ("instant compound"), which has the following structure:



or a pharmaceutically acceptable salt thereof. By my work at Celgene, I am familiar with the instant compound and its pharmacological properties.

Comparison of instant compound with N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisindolin-4-yl)cyclopropanecarboxamide

6. On behalf of Celgene Corporation and at my direction, the instant compound and N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisindolin-4-yl)cyclopropanecarboxamide ("comparative compound"), which has the following structure:



were evaluated for their ability to inhibit TNF alpha and for their anti-angiogenic potential using a vascular endothelial growth factor ("VEGF") induced human umbilical vein endothelial cell ("HUVEC") proliferation assay.

7. With respect to TNF alpha inhibition, the instant compound exhibited an IC_{50} of 50.6 nM, while the comparative compound exhibited an IC_{50} of 8600 nM. In other words, the instant compound was found to be approximately 170 times more potent than the comparative compound in inhibiting TNF alpha.
8. With respect to HUVEC assay, the instant compound exhibited an IC_{50} of 50 nM, while the comparative compound exhibited an IC_{50} of 2600 nM. In other words, the instant compound was found to be approximately 50 times more potent than the comparative compound in inhibiting VEGF-induced HUVEC proliferation.

Comparison of instant compound with thalidomide

9. On behalf of Celgene Corporation and at my direction, the instant compound and thalidomide were tested *in vivo* for anti-angiogenic potential using the VEGF-induced mouse corneal micropocket angiogenesis model.
10. The instant compound inhibited angiogenesis at a rate 26% greater than control after oral dosing of 25 mg/kg, which constitutes significant inhibition of angiogenesis. Thalidomide inhibited angiogenesis at a rate 18% greater than control after oral dosing of 100 mg/kg, which did not constitute significant inhibition.

Conclusion

11. It is my opinion that the results described above are significant and surprising. The instant compound was surprisingly found to be superior to the comparative compound in both TNF alpha inhibition and VEGF-induced HUVEC proliferation.

The instant compound was also surprisingly found to be superior to thalidomide in inhibiting angiogenesis in a VEGF-induced mouse corneal micropocket model. In my opinion, these results could not have been predicted as of the filing date of the application at hand and show the surprising uniqueness of the instant compound with respect to its potential to treat macular degeneration.

12. I, Peter H. Schafer, declare that all statements made herein are of my own knowledge to be true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent that may issue there from.

Dated: 1/29/2010

Peter H. Schafer
PETER H. SCHAFER, Ph.D.

EXHIBIT B

Anti-VEGF therapy: comparison of current and future agents

DJ Pieramici and MD Rabena

Abstract

With the identification of vascular endothelial growth factor (VEGF) and the confirmation of its pathophysiologic link to retinal and choroidal angiogenesis, numerous agents have been designed to inhibit its activity. It is noteworthy that anatomic and visual benefits have been associated with the use of anti-VEGF agents such as pegaptanib (Macugen) and to a greater extent, ranibizumab (Lucentis) and bevacizumab (Avastin), particularly in the management of neovascular age-related macular degeneration (AMD). Clinical trials and case series have confirmed the utility of these agents. However, shortcomings of the current drugs such as short half-life, intravitreal dosing, limited effectiveness in some patients, and potential systemic side effects continue to drive the development of new agents. In this article, we review current anti-VEGF therapies and discuss future developments.

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Keywords: age-related macular degeneration; ranibizumab; bevacizumab; choroidal neovascularization; angiogenesis; anti-vegf

Introduction

The concept that a vascular growth factor is present in neovascular ocular diseases is not new. In the late 1940s, Michelson published a manuscript outlining a concept that a biochemical factor (factor X) was necessary for the normal developmental and growth of the retinal vasculature.¹ This same growth factor, Michelson proposed, was likely necessary for pathologic angiogenesis as well, and that its presence in this setting was the result of changes

in metabolism in the retina. For years ophthalmologists have used pan-retinal laser photocoagulation (PRP) to effectively treat neovascular retinopathy. It has been assumed that the mechanism of action PRP laser has been to reduce the intraocular levels of this, yet unidentified, vascular growth factor. In 1971, Folkman² published a paper in the *New England Journal of Medicine* proposing a theory that tumour angiogenesis was necessary for tumour growth and that inhibition of angiogenesis could be therapeutic. His team identified a factor, tumour angiogenic factor that they proposed as a candidate for therapeutic anti-angiogenesis. Many in the field did not initially welcome these concepts, very few others outside of Folkman's laboratory pursued tumour angiogenesis for the next 10 years. In 1983, Senger *et al.*³ identified in tumour ascites fluid a 42 kDa protein and vascular permeability factor. In 1989, Ferrera⁴ published results identifying and purifying a novel glycoprotein growth factor specific for endothelial cells that was secreted by pituitary follicular cells. Their glycoprotein is likely the same molecule previously identified by Senger *et al.* Leung⁵ and simultaneously Keck *et al.*⁶ cloned similar molecules: vascular endothelial growth factor (VEGF) and vascular permeability factor. Using antibody techniques specific inhibitors could now be produced ushering in a new era in the treatment of cancer and retinal angiogenesis.

In 2001, The Food and Drug Administration (FDA) approved the first anti-VEGF agent, pegaptanib (Macugen) for the treatment of neovascular age-related macular degeneration (AMD). Though limited in its effectiveness in the treatment of neovascular AMD, its approval signalled the beginning of a new generation in AMD treatment, the era of anti-VEGF therapy.

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Vascular endothelial growth factor pharmacologic considerations

Vascular endothelial growth factor (VEGF)-A is a major regulator of angiogenesis and vascular permeability in the eye for physiologic as well as pathologic processes. It also plays a role as a survival factor for many cells. VEGF has been implicated in ocular diseases ranging from diabetic retinopathy to AMD. VEGF-A, the molecule implicated in eye diseases is a member of a gene family which includes: VEGF B, C, D, and placental growth factor. There are also multiple isoforms of VEGF-A based on the number of amino acids included in their structure. Some are bound to the extracellular matrix (ie VEGFs 189 and 206) and cell surfaces, while smaller isoforms (ie VEGF 121) are diffusible. The larger isoforms can be cleaved by fibrinolysis to produce biologically active VEGF 110. VEGF-A binds to two types of receptors, VEGFR1 and VEGFR2, both are protein kinase-activating receptors. It is the binding of the VEGFR2 that is important for ocular neovascularization.

Rational approaches to block VEGF activity would include inhibition of VEGF, VEGFR2 or protein kinase activity amongst others. Two agents have been approved in the United States by the FDA for use in neovascular AMD, pegaptanib (Macugen) and ranibizumab (Lucentis). A third drug bevacizumab (Avastin) has been approved for the use in oncology but is also widely used 'off label' in the treatment of neovascular AMD, diabetic retinopathy and other retinal vascular and proliferative disease processes.

Pegaptanib

Pegaptanib (Macugen) was the first anti-VEGF agent approved. Pegaptanib is a 28-base ribonucleic aptamer, a small fragment of RNA that binds proteins with high affinity. *In vivo*, pegaptanib binds to the extracellular VEGF165 isoform. This interaction inhibits the VEGF from binding and activating the VEGFR2 receptor. Pegaptanib selectively binds to only the 165 isoform. This may explain its limited efficacy compared to agents that are capable of pan-isoform suppression. This selective targeting might also be advantageous in reducing suppression of systemic or ocular VEGF necessary for normal function, making it a safer choice. This concept however has not been validated.

Two concurrent phase III randomized multicentre dose-ranging sham-controlled clinical trials demonstrated the efficacy of pegaptanib in the treatment of neovascular AMD. (VISION Trials).⁷ In total, 1186 patients were enrolled in these two trials in which the patient received pegaptanib or sham intravitreally every 6 weeks for 48 weeks. The primary efficacy end point of

these trials were the percentages of patients in each group losing less than 15 letters of visual acuity at 1 year. This was achieved in 70% of the pegaptanib treated (0.3 mg dose) vs 55% of the sham-treated patients ($P < 0.001$). However, this treatment resulted in improvements in visual acuity in few patients. On average, patients continued to lose vision during the first 2 years of the study, but significantly less vision as compared to the sham group. Though pegaptanib was well tolerated, with few serious local or systemic side effects, the visual outcomes were disappointing. In fact, the outcomes were similar to the existing standard treatment, photodynamic therapy with verteporfin. Pegaptanib however was approved for a larger percentage of patients presenting with neovascular AMD, and did not appear to be limited by angiographic subtype. With the advent of much more efficacious agents (ranibizumab and bevacizumab), the use of pegaptanib has fallen precipitously. Given its long record of safe use and theoretical reduced risk of side effects associated with pan-VEGF suppression, some have proposed a role for pegaptanib as maintenance therapy following induction with a pan-VEGF agent. Such an approach, though rational, has not been proven efficacious or safer to date. Trials are ongoing.

Ranibizumab and bevacizumab

It is impossible to talk about ranibizumab in isolation of bevacizumab in the treatment of neovascular AMD. Currently in the United States, according to the preferences and trends (PAT) survey of the American Society of Retina Specialist, these drugs are used in equal frequency to treat neovascular complications of AMD. However, only ranibizumab has received FDA approval, though Medicare has agreed to pay for either drug for appropriate AMD patients. The availability of both drugs has generated some controversy as Genentech has attempted to limit access of bevacizumab for ocular indications, favouring the significantly more expensive alternative ranibizumab. Whether the efficacy and safety of bevacizumab equals that of ranibizumab remains to be determined but there is rational to presuppose that any differences may be small.

Both ranibizumab and bevacizumab were derived from the same murine antibody to VEGF. Bevacizumab is the humanized full-length antibody, whereas ranibizumab is the Fab fragment that is humanized and affinity matured, so that its binding affinity is approximately 20 times that of bevacizumab. Bevacizumab (Avastin) was developed by Genentech to be used to treat cancer and initially approved by the FDA for use as an adjunct in patients with metastatic colon cancer.

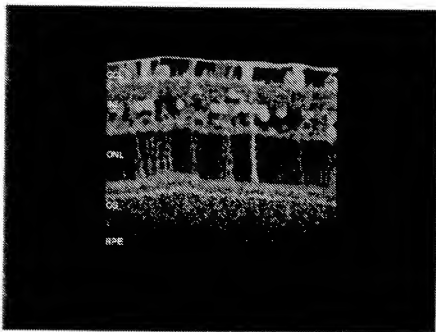


Figure 1 Laser scanning confocal microscope image of a rabbit eye at 24h after intravitreal injection of bevacizumab. Specific antibody labelling was present along the internal limiting membrane (ILM), the ganglion cell (GC), inner nuclear layer (INL) as well as inner and outer segment (OS) layers of photoreceptors. Courtesy of Robert Avery, MD (California Retina Consultants and UCSB Neuroscience Research Institute Retinal Cell Biology Lab).

Early penetration studies using full-length antibodies and the Fab fragment ranibizumab (Lucentis) seemed to indicate that the full-length antibody penetrated the retina poorly.⁸ Conversely, the high-affinity Fab fragment penetrated the neurosensory retina, suggesting that this molecule would be more effective in the treatment of neovascular AMD. Recent penetration studies refute the earlier studies of Mordenti, demonstrating rapid full-thickness penetration^{9,10} (Figure 1). Despite this, the Fab fragment (ranibizumab) may offer a few additional advantages over bevacizumab including higher affinity binding and potentially less immunogenicity as it lacks the Fc portion of a full-length antibody.

Recent half-life data suggest an advantage of the larger full-length antibody with increased half-life in the vitreous, retina, and choroid.^{11,12} On the other hand, when considering toxicity and systemic exposure, the longer systemic exposure of bevacizumab may be a disadvantage.

Ranibizumab

A number of phase III clinical trials (ANCHOR, MARINA, PIER) have validated the use of ranibizumab in the treatment of all angiotrophic subtypes of choroidal neovascularization.^{13,14}

The MARINA trial investigated ranibizumab (0.3 and 0.5 mg doses) *vs* placebo in patients with occult and minimally classic subfoveal choroidal neovascularization.¹⁴ The primary efficacy end point of this trial was the percentage of patients losing less than 15 early treatment of diabetic retinopathy study (ETDRS) letters with 90% of patients meeting this criteria at 2 years following enrollment. More striking however, on average, patients receiving ranibizumab experienced 6.5 ETDRS letters of improvement at 2 years, while the placebo group lost nearly 15 letters. Equally exciting, 1 of 3 of patients experienced improvement of 3 or more lines of vision improvement and at 2 years, 42% of the patients had vision of 20/40 or better Snellen equivalent. These results demonstrated for the first time, average visual improvement, a new milestone in AMD care (Figure 2).

The ANCHOR trial investigated ranibizumab *vs* photodynamic therapy (PDT) (Visudyne) for the treatment of subfoveal classic choroidal neovascularisation (CNV) in AMD.¹³ The results of the ANCHOR trial were similar with the ranibizumab group experiencing an average vision improvement of 11.3 letters at 12 months *vs* the PDT group experiencing a loss of 9.5 letters, similar to the previously reported treatment of AMD with PDT trial results¹⁵ (Figure 2). At 2 years,

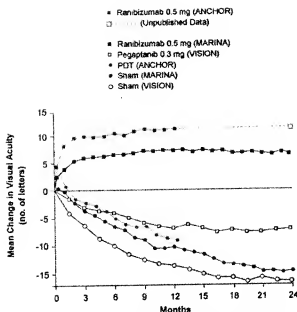


Figure 2 Mean change in visual acuity through 24 months for subjects in MARINA, ANCHOR, TAP and VISION trials.

over 40% of the ranibizumab vs 6% of the PDT-treated patients experienced three or more lines of vision improvement, with 38 vs 6% of the ranibizumab and PDT groups respectively obtaining vision of 20/40 or better.¹³

In the ANCHOR and MARINA trials, patients were treated every month for 2 years with an intravitreal injection. The PIER trial investigated ranibizumab given every month for the first three injections followed by quarterly injections (unpublished). The vision improved on average in the PIER ranibizumab group similar to the patients treated in the ANCHOR and MARINA trials during the monthly injection phase. However, much of the initial improvements in vision were lost during the quarterly injection period so that at year one the average vision returned to baseline. Nonetheless, the sham injection group lost 16 letters during the first year.

In a small investigator sponsored study (PRONTO), Rosenfeld *et al* demonstrated that results similar to the ANCHOR and MARINA trial could be obtained at 1 and 2 years using three initial monthly injections followed by monthly PRN (as needed) injections (unpublished). During the PRN period re-treatment was determined by vision, clinical evaluation, and optical coherence tomography (OCT) findings. On average, patients treated following the PRONTO protocol required five to six injections during the first year (vs 12 in the ANCHOR and MARINA). Although this trial included only 40 patients and no control group, the results have

compelled most retina specialists to follow a similar protocol when treating their patients.

The safety of intravitreal ranibizumab has been confirmed in the initial clinical trials and the phase IV SAILOR trial (unpublished). The main ocular risk is the development of endophthalmitis. In a cumulative study (ANCHOR and MARINA data combined), investigating the risk of adverse ocular events, endophthalmitis occurred in 0.5–1.6% of the ranibizumab-treated patients during the first 2 years of treatment ($N=754$) and serious non-infectious uveitis occurred in 0.8–1.1% of the treated patients (unpublished data).

Serious systemic side effects such as systemic hypertension and arterial thromboembolic events are of concern following high-dose intravenous administration of anti-VEGF agents such as bevacizumab. Whether such complications are possible with intravitreal delivery of drugs that are dosed at levels hundreds of times lower remains a concern. In the combined analysis of the ANCHOR and MARINA trials, the rates of hypertension and arterial thromboembolic events were similar between the treatment and control groups. In this 2-year analysis there was however an increased rate of non-ocular haemorrhages in the treated patients (9%, $N=754$) vs (5%, $N=379$) the control group (unpublished). Overall the rates of thromboembolic events reported amongst patients receiving ranibizumab in all the trials including the phase IV SAILOR trial appear very similar to age-matched controls. It will require significantly larger numbers of patients to determine whether or not small differences exist.

Bevacizumab

Though not specifically developed for intraocular use, bevacizumab has demonstrated biologic activity akin to ranibizumab in the treatment of neovascular AMD. The use of bevacizumab was spawned from the excitement investigators generated from the ranibizumab clinical trials. As the clinical effect of ranibizumab was so apparent, one need not wait for the statistical analysis to be convinced that a positive biologic effect was occurring. Unfortunately, unless the patients were part of the ongoing clinical trials, ranibizumab was not available at that time. Fortunately, bevacizumab had been recently FDA approved and was available for the use in colorectal cancer. This made it available to physicians to be used off-label for other indications. A group of investigators in Miami first demonstrated that intravenous bevacizumab could be useful in the treatment of choroidal neovascularization; however, systemic side effects were a limiting factor.¹⁶ Rosenfeld and co-workers then demonstrated that intravitreal delivery was a possibility in two case reports.^{17,18} Following this, a number of

investigators, including our group, became early adaptors of intravitreal bevacizumab.^{19,20} Our initial series of patients with neovascular AMD treated with intravitreal bevacizumab was encouraging with rapid reduction in subretinal fluid, macular oedema, and pigment epithelial detachments in most treated patients¹⁹ (Figure 3). This was often associated with visual improvement if the lesions treated were not too mature (Figure 4). Again, the apparent biologic effect generated excitement amongst clinicians and bevacizumab was

rapidly accepted worldwide as a treatment for neovascular AMD. It can be argued that bevacizumab for AMD was one of the most successful drug launches in history and it occurred without the financial support of the pharmaceutical industry. To date, numerous retrospective and a few prospective trials have all suggested positive results in treated patients with reduction in leakage detected by OCT and fluorescein angiography. No obvious safety issue disparate from those reported for ranibizumab have been identified, though a longer systemic half-life might increase the length of time that a patient is exposed to such side effects. A registry of 5228 patients (7113 injections) treated at 70 separate centres with bevacizumab has been collected, failing to demonstrate obvious safety outliers.²¹ Retrospective reviews and registry data are at risk of sampling bias, incomplete reporting, and short follow-up, so definite safety conclusions cannot be drawn.

How does one determine whether to suggest ranibizumab or bevacizumab for a given patient with CNV? In reality, most decisions come down to finances with the cost of ranibizumab being 40 times that of bevacizumab in the United States.

No one can argue that the available clinical science favours the use of bevacizumab over ranibizumab. The ranibizumab phase III clinical trials are the best information indicating the safety and efficacy of anti-VEGF therapy for AMD. All other currently available clinical data falls short of these trials. To suggest that bevacizumab or ranibizumab has a clear efficacy or safety advantage is speculative. Two clinical trials, one in England and one in the United States (CATT Trial) are designed to investigate in a head-to-head fashion ranibizumab and bevacizumab in the treatment of choroidal neovascularization. In addition, the CATT trial will also determine whether or not there is a significant difference between monthly or PRN dosing. However, it will likely be 1 or 2 years before preliminary data from these trials are available.

Future anti-VEGF agents

A number of novel anti-VEGF agents are currently in phase III clinical trials and if they demonstrate efficacy similar to ranibizumab, may come to market in the next few years. One such agent is VEGF trap.²² VEGF trap is essentially a soluble VEGF receptor. When injected into the vitreous, VEGF trap acts as a decoy receptor binding-free VEGF. VEGF trap is smaller than a full-length antibody and should penetrate all layers of the retina. It has a higher affinity than the currently available anti-VEGF agents and blocks all isoforms of VEGF. Phase I trials with intravenous administration demonstrated a positive biologic effect with the reduction of retinal

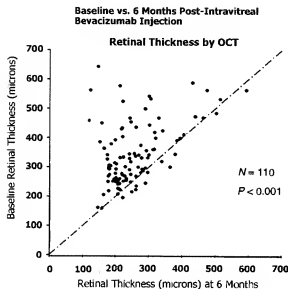


Figure 3 Scatter plot of change in central subfield thickness (microns) 6 months after injection of bevacizumab, as measured by optical coherence tomography.

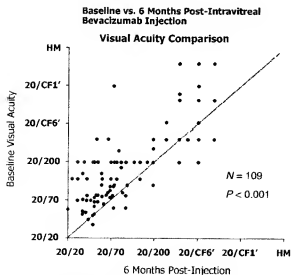


Figure 4 Scatter plot of change in Snellen visual acuity 6 months after injection(s) of bevacizumab.

thickness but also a dose-dependant increase in blood pressure in patients receiving VEGF trap (unpublished data). In a phase I/II study of intravitreal VEGF trap (N = 21) there were no systemic or ocular side effects (unpublished data). Treated patients experienced a reduction in macular thickening, lesion size, visual improvement on average of 4.8 ETDRS letters, and 95% avoided 15 or more letters of vision loss at 6 weeks following a single injection. Phase III trials are underway.

Another novel strategy to inhibit VEGF utilizes small interfering RNA technology (siRNA). siRNA involves short double-stranded RNA fragments. These siRNA become incorporated into the RNA-induced silencing complex (RISC). When activated, the RISC binds to the target sequence resulting in mRNA cleavage and silence of the gene; two such siRNA molecules are under investigation bevasiranib and SIRNA-027. Bevasiranib is designed to inhibit production of VEGF, while SIRNA-027 is directed against the VEGF receptor. Phase I/II trials have been encouraging; however, treated eyes did not experience a statistically significant improvement in distant visual acuity (unpublished). A phase III trial of bevasiranib (COBALT) is underway to see if it might be effectively used in conjunction with ranibizumab to reduce the need for additional treatment.

We have entered the era of anti-VEGF therapy in the treatment of choroidal neovascularization in patients with AMD. This treatment has resulted in unprecedented visual and anatomic outcomes far outpacing other available treatments. Today physicians and patients can expect visual stabilization in most patients and visual improvement in many, particularly, if treatment is begun early in the course of the disease. Current research now focuses on ways of increasing the durability of effect, reducing side effects, and facilitating delivery. The bar has been set quite high now with medications such as ranibizumab and bevacizumab, but advances in therapy can be expected in the next 5 years.

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EXHIBIT C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Zeldis	Confirmation No.:	1866
Serial No.:	10/699,110	Art Unit:	1612
Filed:	October 30, 2003	Examiner:	Fay, Zohreh A.
For:	METHODS FOR THE TREATMENT AND MANAGEMENT OF MACULAR DEGENERATION USING CYCLOPROPYL-N-(2-[(1S)-1-(3- ETHOXY-4-METHOXYPHENYL)-2- (METHYLSULFONYL)ETHYL]-3- OXOISOINDOLINE-4- YL)CARBOXAMIDE	Docket No: CAM:	9516-083-999 501872-999082

DECLARATION BY PETER H. SCHAFER, PH.D. UNDER 37 C.F.R. § 1.132

Mail Stop AF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, PETER H. SCHAFER, Ph.D., declare as follows:

1. I have personal knowledge of the matters contained herein, or know them by my review of U.S. Application No. 10/699,110 or my review of studies performed at the Vanderbilt University School of Medicine, Departments of Pathology and Ophthalmology.

I. Background

2. I received my Bachelor of Science degree in Biological Chemistry from the University of Chicago, Chicago, Illinois in 1991. I received my Ph.D. degree from the Department of Biochemistry, Molecular Biology, and Cell Biology at Northwestern University, Evanston, Illinois in 1996.

3. From 1996 to 1999, I was a post-doctoral researcher at The R.W. Johnson Pharmaceutical Research Institute in Raritan, New Jersey. From 1999 to present, I have been employed by Celgene Corporation, Summit, New Jersey, as a Research Scientist, a Senior

Research Scientist, a Group Leader, then as an Associate Director of Biology. Currently, I hold a position of the Director of Biology in the Department of Drug Discovery at Celgene Corporation.

4. I have published in peer-reviewed journals and made presentations at various academic conferences. I am also a named co-inventor of several patents and patent applications, including applications and patents owned by Celgene Corporation.

5. I am affiliated with the International Society for the Biological Treatment of Cancer, American Association for the Advancement of Science, and American Association of Immunologists. I have been serving as a reviewer for academic journals such as the Journal of Pharmacology and Experimental Therapeutics, European Journal of Hematology, and Leukemia and Lymphoma. My curriculum vitae is attached hereto as Exhibit A.

II. Evaluation of cyclopropyl-N-(2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindoline-4-yl)carboxamide

6. On the basis of my review of U.S. Application No. 10/699,110, I understand that the pending claims in the present application recite, *inter alia*, methods of treating macular degeneration comprising administering cyclopropyl-N-(2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindoline-4-yl)carboxamide ("the instant compound").

7. I understand that Celgene Corporation commissioned the Vanderbilt University School of Medicine, Departments of Pathology and Ophthalmology, to evaluate the efficacy of the instant compound in the inhibition of choroidal neovascularization and to compare any such efficacy to Lucentis[®], a FDA-approved drug for the treatment of wet age-related macular degeneration.

A. Protocol

8. I understand that the tests utilized the laser-induced rupture of Bruch's membrane choroidal neovascularization ("CNV") model. These tests were performed on both mice and rats. Specifically, the tests were performed on Brown Norway rats and C57BL/6J mice (males; 4-6 weeks of age).

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9. I understand that laser-induced rupture of Bruch's membrane was used to generate CNV. The animals were anesthetized with xylazine hydrochloride (10 mg/kg) and ketamine (50 mg/kg), and the pupils were dilated with 1% tropicamide (Alcon Labs, Inc.; Fort Worth, TX). A hand-held cover slide was used as a contact lens, and an argon laser photocoagulator (532 nm) mounted on a slit-lamp (Coherent Novus Omni, Lumenis Inc.; Santa Clara, CA) was employed to create four burns centered around the optic nerve head in the retinal mid-periphery (50 μ m spot size, 0.1 sec duration, 360 mW) in the rats. For the mice, the procedures were similar with the exception that the laser energy was set to 260 mW. This procedure causes a bubble at the time of laser application to indicate rupture of Bruch's membrane. Burns not resulting in a bubble were not included in the study. Immediately after laser treatment, the rats and mice were divided into four groups for the administration of drugs.

10. I understand that the dosing regime for the mice was as follows: (1) oral administration of the instant compound at 5 mg/kg BID; (2) oral administration of the instant compound at 15 mg/kg BID; (3) oral administration of the vehicle BID; and (4) intravitreal administration of 2 μ L Lucentis[®] (10 mg/mL, positive control treatment) at 1, 3, and 7 days following laser treatment.

11. I understand that the dosing regime for the rats was as follows: (1) oral administration of the instant compound at 10 mg/kg BID; (2) oral administration of the instant compound at 25 mg/kg BID; (3) oral administration of the vehicle BID; and (4) intravitreal administration of 5 μ L Lucentis[®] (10 mg/mL, positive control treatment) at 1, 3, and 7 days following laser treatment.

12. I understand that fourteen days following laser application, the rats and mice were sacrificed to measure the extent of CNV at the Bruch's membrane rupture sites. The eyes of the animals were removed, and choroid-sclera-retinal pigment epithelium flat-mounts were prepared by removing the cornea and lens in 10% phosphate-buffered formalin. After dissecting the retina from the eyecup and discarding it, radial cuts were made in all four quadrants in order to flatten the remaining tissue. The flattened choroid-sclera-retinal pigment epithelium tissue was then mounted in Gel Mount (Biomedix; Victoria, Australia). Choroidal neovascular growth was assessed at two weeks post-laser treatment in

fluorescently-stained flat-mounts, using published methods. See, e.g., Bora *et al.*, *J. Immunol.* 2005, 174(1):491-7. Endothelial cells were identified using FITC-conjugated Griffonia simplicifolia isolectin B₄ (Sigma-Aldrich, Inc.), and the elastin of the surrounding extracellular matrix was stained using donkey anti-elastin antibody conjugated to Cy3 (Santa Cruz Biotech, Inc.). Areas of abnormal vascular growth were measured via computer-assisted image analysis using high-resolution digital images of the stained choroid-sclera-retinal pigment epithelium flat-mounts. The effects of the various treatments on the progression of laser-induced CNV were determined using an analysis of variance (ANOVA) and the Dunnett's post-hoc test with significance set to $P < 0.05$. The sizes of the four lesions were averaged for each eye, the two eyes were averaged for each animal, and the values derived from each animal were averaged for each treatment group. The treatment group averages were used for the final analysis.

B. Results

13. I understand that with regard to the tests on mice, oral administration of the instant compound resulted in significant inhibition of laser-induced CNV. Specifically, administration of the instant compound at 5 mg/kg BID resulted in a 69% reduction in the neovascular area, and the administration at 15 mg/kg resulted in a 73% reduction in the neovascular area ($P < 0.002$). Moreover, the observed inhibition resulting from the administration of the instant compound was remarkably higher than the inhibition resulting from the intravitreal injection of Lucentis[®], which was 36% ($P = 0.0913$ under Dunnett's Method; $P = 0.0423$ under Student's *t*-test). See Exhibit B, Figure 1.

14. I understand that with regard to the tests on rats, oral administration of the instant compound resulted in significant inhibition of laser-induced CNV. Specifically, administration of the instant compound at 10 mg/kg BID resulted in a 61% reduction in the neovascular area, and administration at 25 mg/kg BID resulted in a 65% reduction in the neovascular area ($P < 0.0001$). Moreover, the observed inhibition resulting from the administration of the instant compound was comparable to the inhibition resulting from the intravitreal injection of Lucentis[®], which was 62% ($P < 0.0001$). See Exhibit B Figure 2.

III. Conclusion

15. It is my opinion that the observed efficacy of the instant compound in rat and mice tests is significant and surprising. Specifically, it is significant and surprising that oral administration of the instant compound performed as well as or better than the intravitreal injection of Lucentis[®], which represents the current standard of clinical care in connection with the treatment of wet age-related macular degeneration.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

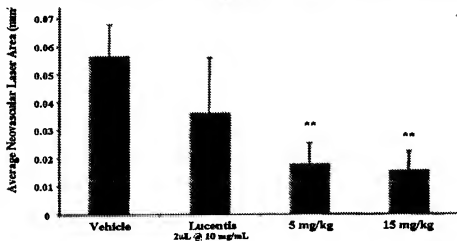
Dated: 5 August 2008

Peter H. Schaffer
PETER H. SCHAFER, Ph.D.

EXHIBIT B

Figure 1

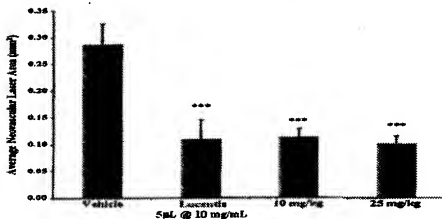
Histogram of Instant Compound on Laser-Induced Choroidal Neovascularization Areas in Mice



Asterisks (**) represent significance levels of $P < 0.002$ vs. vehicle control.

Figure 2

Histogram of Instant Compound on Laser-Induced Choroidal Neovascularization Areas in Rats



Asterisks (**) represent significance levels of $P < 0.0001$ vs. vehicle control.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Zeldis	Confirmation No.:	1866
Serial No.:	10/699,110	Art Unit:	1612
Filed:	October 30, 2003	Examiner:	Fay, Zohreh A.
For:	METHODS FOR THE TREATMENT AND MANAGEMENT OF MACULAR DEGENERATION USING CYCLOPROPYL-N-[2-(1S)- 1-(3-ETHOXY-4- METHOXYPHENYL)-2- (METHYLSULFONYL)ETHYL]-3- OXOISOINDOLINE-4- YL; CARBOXAMIDE	Attorney Docket No: (CAM:	9516-083-999 501872-999082)

DECLARATION BY PETER H. SCHAFER, PH.D. UNDER 37 C.F.R. 1.132

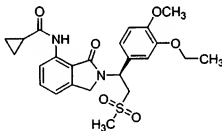
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Peter H. Schafer, Ph.D., declare and state that:

1. I received my Bachelor of Science degree in Biological Chemistry from University of Chicago, Chicago, Illinois in 1991. I received my Ph.D. degree from the Department of Biochemistry, Molecular Biology, and Cell Biology at Northwestern University, Evanston, Illinois in 1996.
2. From 1996 to 1999, I was a post-doctoral researcher at The R.W. Johnson Pharmaceutical Research Institute in Raritan, New Jersey. From 1999 to present, I have been employed by Celgene Corporation, Summit, New Jersey, as a Research Scientist, a Senior Research Scientist, a Group Leader, an Associate Director of Biology, and then as a Director of Biology in the Department of Drug Discovery at Celgene Corporation. Currently, I hold the position of Director of Translational Development at Celgene.

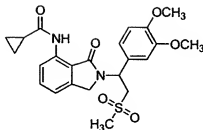
3. I have published in peer-reviewed journals and made presentations at various academic conferences. I am also a named co-inventor of several patents and patent applications owned by Celgene Corporation and relating to immunomodulatory compounds and phosphodiesterase IV ("PDE IV") inhibitors.
4. I have been serving as a reviewer for journals such as Journal of Pharmacology and Experimental Therapeutics, Life Sciences, and Clinical Medicine: Therapeutics.
5. I am familiar with the disclosure and claims of the above-identified patent application ("the '110 application"). I understand that the pending claims recite, *inter alia*, methods of treating macular degeneration, comprising administering a therapeutically effective amount of cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl} carboxamide ("instant compound"), which has the following structure:



or a pharmaceutically acceptable salt thereof. By my work at Celgene, I am familiar with the instant compound and its pharmacological properties.

Comparison of instant compound with N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisindolin-4-yl)cyclopropanecarboxamide

6. On behalf of Celgene Corporation and at my direction, the instant compound and N-(2-(1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl)-3-oxoisindolin-4-yl)cyclopropanecarboxamide ("comparative compound"), which has the following structure:



were evaluated for their ability to inhibit TNF alpha and for their anti-angiogenic potential using a vascular endothelial growth factor ("VEGF") induced human umbilical vein endothelial cell ("HUVEC") proliferation assay.

7. With respect to TNF alpha inhibition, the instant compound exhibited an IC_{50} of 50.6 nM, while the comparative compound exhibited an IC_{50} of 8600 nM. In other words, the instant compound was found to be approximately 170 times more potent than the comparative compound in inhibiting TNF alpha.
8. With respect to HUVEC assay, the instant compound exhibited an IC_{50} of 50 nM, while the comparative compound exhibited an IC_{50} of 2600 nM. In other words, the instant compound was found to be approximately 50 times more potent than the comparative compound in inhibiting VEGF-induced HUVEC proliferation.

Comparison of instant compound with thalidomide

9. On behalf of Celgene Corporation and at my direction, the instant compound and thalidomide were tested *in vivo* for anti-angiogenic potential using the VEGF-induced mouse corneal micropocket angiogenesis model.
10. The instant compound inhibited angiogenesis at a rate 26% greater than control after oral dosing of 25 mg/kg, which constitutes significant inhibition of angiogenesis. Thalidomide inhibited angiogenesis at a rate 18% greater than control after oral dosing of 100 mg/kg, which did not constitute significant inhibition.

Conclusion

11. It is my opinion that the results described above are significant and surprising. The instant compound was surprisingly found to be superior to the comparative compound in both TNF alpha inhibition and VEGF-induced HUVEC proliferation.

The instant compound was also surprisingly found to be superior to thalidomide in inhibiting angiogenesis in a VEGF-induced mouse corneal micropocket model. In my opinion, these results could not have been predicted as of the filing date of the application at hand and show the surprising uniqueness of the instant compound with respect to its potential to treat macular degeneration.

12. I, Peter H. Schafer, declare that all statements made herein are of my own knowledge to be true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent that may issue there from.

Dated: 1/29/2010

Peter H. Schafer
PETER H. SCHAFER, Ph.D.